PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Docket No: **Q94898**
Risto KOSTIAINEN et al	Conf. No.: **6385**
Appln. No.: **10/579,225**	Group Art Unit: **2881**
Filed: **May 12, 2006**	Examiner: **Unassigned**

For: **METHOD AND APPARATUS FOR MASS SPECTROMETRIC ANALYSIS**

PETITION UNDER 37 C.F.R. 1.47 (a)

ATTN: BOX MISSING PARTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants hereby petition under 37 C.F.R. 1.47(a) to be permitted to proceed with prosecution of the above-identified application absent the signature of one of the joint inventors, Seppo Martilla. The grounds for the petition are set forth below and supported by the accompanying documentary evidence.

As explained in the accompanying executed Declaration of Anu Leinonen, a Director at Licenta Oy (the Assignee of the above-identified application), Mr. Martilla, a co-inventor, was provided with a copy of the application, Declaration and Power of Attorney and Assignment, and requested to execute the same. Mr. Martilla refused to execute the formal papers saying that his initial assignment of his rights (see Appendix C of Leinonen's Declaration) cleared him of his responsibilities in this matter.

The refusing inventor's last known address is:

Mr. Seppo Martilla
Maaníituntíe 16
01900 Nurmijärvi, FINLAND

A check for the petition fee of $130.00 under 37 C.F.R. § 1.17(h) is attached. The U.S. Patent and Trademark Office is also hereby authorized to charge any fees necessary for the

continued pendency of the above-identified application to Applicants' Deposit Account No. 19-4880.

Respectfully submitted,

Gordon Kit
Registration No. 30,764

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WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: 3/24, 2008

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Risto KOSTIAINEN et al

Conf. No.: 0000

Appln. No.: __/___,___

Group Art Unit: 0000

Filed: May 12, 2006

Examiner: Unassigned

For: METHOD AND APPARATUS FOR MASS SPECTROMETRIC ANALYSIS

DECLARATION IN SUPPORT OF INVENTOR'S REFUSAL TO SIGN DECLARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Anu Leinonen, hereby declare and state the following:

1. I reside at Runebergingatu 55a A16, 00260 Helsinki, FINLAND.

2. I work for Licentia Oy, where I hold a position as Director.

3. On May 8, 2006, I forwarded to Mr. Seppo Marttila a copy of the above-referenced patent application and a Declaration and Power of Attorney and Assignment therefor (attached as Exhibit A). A copy of my letter (along with an English translation thereof) dated May 8, 2006, forwarding these papers to Mr. Marttila and requesting that he execute them and return the same to me is attached hereto as Exhibit B.

4. On May 9, 2006, I was contacted by telephone by Mr. Marttila. He informed me at that time that he would not sign the Declaration and Power of Attorney and Assignment because he does not want to have anything to do with the invention or patent application anymore; that he assigned all

DECLARATION IN SUPPORT OF INVENTOR'S REFUSAL TO SIGN DECLARATION
U.S. Appln. No. __/___,___ (Q94898)

rights to the invention to the other three inventors (Risto Kostiainen, Samuli Franssila and Tapio Kotiaho) on November 11, 2003; and he considers that the assignment clears all of his responsibilities regarding this matter.

5. A copy of the November 11, 2003, Assignment (along with an English translation thereof) is attached hereto as Exhibit C.

6. Also, attached hereto as Exhibit D is a document dated November 11, 2006 (along with an English translation of the relevant portions thereof), indicating that Risto Kostiainen, Samuli Franssila and Tapio Kotiaho sold all of their rights in the invention to Licentia Oy.

7. To the best of my knowledge, Mr. Martilla's last known address is Maanituntie 16, 01900 Nurmijärvi, FINLAND.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: June 2, 2006

Name: Anu Leinonen

EXHIBIT A

DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

As a below named inventor, I hereby declare that: My residence, mailing address, and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

KOSTIAINEN, Risto, Väinö Auerinkatu 7 F 72, FI-00560 Helsinki, Finland; FRANSSILA, Samuli, Tukholmankatu 7 C19, FI-00270 Helsinki, Finland; KOTIAHO, Tapio, Otsonkalliontie 3 S 139, FI-02110 Espoo, Finland and MARTTILA, Seppo, Maaniituntie 16, FI-01900 Nurmijärvi, Finland

the application of which
☐ is attached hereto

OR

☒ was filed on November 15, 2004 as United States Application Number or PCT International Application Number PCT/FI2004/000683 (Confirmation No. _____), and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part application(s), material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application(s) which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application(s) having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date	Priority Claimed Yes	Priority Claimed No
20031658	Finland	November 14, 2003	☒	☐

I hereby claim domestic priority benefits under 35 United States Code §120 of any United States application(s), §119(e) of any United States provisional application(s), or §365(c) of any PCT International application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in a listed prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge my duty to disclose any information material to the patentability of this application as defined in 37 C.F.R. 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Prior U.S. or International Application Number(s)	U.S. or International Filing Date	Status
PCT/FI2004/000683	November 15, 2004	pending

I hereby appoint all attorneys of **SUGHRUE MION, PLLC** who are listed under the USPTO Customer Number shown below as my attorneys to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith, recognizing that the specific attorneys listed under that Customer Number may be changed from time to time at the sole discretion of Sughrue Mion, PLLC, and request that all correspondence about the application be addressed to the address filed under the same USPTO Customer Number.

23373

PATENT TRADEMARK OFFICE

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR:

Given Name (first and middle [if any]) Risto		Family Name or Surname KOSTIAINEN	
Inventor's Signature			Date
Residence: City Helsinki	State	Country Finland	Citizenship Finnish
Mailing Address: Väinö Auerinkatu 7 F 72			
City Helsinki	State	Zip FI-00560	Country Finland

NAME OF SECOND INVENTOR:

Given Name (first and middle [if any]) Samuli		Family Name or Surname FRANSSILA	
Inventor's Signature			Date
Residence: City Helsinki	State	Country Finland	Citizenship Finnish
Mailing Address: Tukholmankatu 7 C 19			
City Helsinki	State	Zip FI-00270	Country Finland

NAME OF THIRD INVENTOR:

Given Name (first and middle [if any]) Tapio		Family Name or Surname KOTIAHO	
Inventor's Signature			Date
Residence: City Espoo	State	Country Finland	Citizenship Finnish
Mailing Address: Otsonkalliontie 3 S 139			
City Espoo	State	Zip FI-02110	Country Finland

NAME OF FOURTH INVENTOR:

Given Name (first and middle [if any]) Seppo		Family Name or Surname MARTTILA	
Inventor's Signature			Date
Residence: City Nurmijärvi	State	Country Finland	Citizenship Finnish
Mailing Address: Maaniituntie 16			
City Nurmijärvi	State	Zip FI-01900	Country Finland

NAME OF FIFTH INVENTOR:

Given Name (first and middle [if any])		Family Name or Surname	
Inventor's Signature			Date
Residence: City	State	Country	Citizenship
Mailing Address:			
City	State	Zip	Country

For Non-U.S. Clients

Assignment

Whereas, I/We, KOSTIAINEN, Risto of Helsinki, Finland; FRANSSILA, Samuli of Helsinki, Finland; KOTIAHO, Tapio of Espoo, Finland and MARTTILA, Seppo of Nurmijärvi, Finland

hereinafter called assignor(s), have invented certain improvements in
Method and Apparatus For Mass Spectrometric Analysis

and executed an application for Letters Patent of the United States of America therefor on _____; and

Whereas, LICENTIA OY
Tukholmankatu 8 A
FI-00290 Helsinki
Finland

(assignee), desires to acquire the entire right, title, and interest in the application and invention, and to any United States patents to be obtained therefor;

Now therefore, for valuable consideration, receipt whereof is hereby acknowledged,

I/We, the above named assignor(s), hereby sell, assign and transfer to the above named assignee, its successors and assigns, the entire right, title and interest in the application and the invention disclosed therein for the United States of America, including the right to claim priority under 35 U.S.C. §119, and I/we request the Director – U.S. Patent and Trademark Office to issue any Letters Patent granted upon the invention set forth in the application to the assignee, its successors and assigns; and I/we will execute without further consideration all papers deemed necessary by the assignee in connection with the United States application when called upon to do so by the assignee.

I/We hereby authorize and request our attorneys SUGHRUE MION, PLLC of 2100 Pennsylvania Avenue, NW, Washington, DC 20037-3213 to insert here in parentheses (Application number _____ and Confirmation number _____, filed _____) the filing date and application number of said application when known.

Date: _____
s/ KOSTIAINEN, Risto

Date: _____
s/ FRANSSILA, Samuli

Date: _____
s/ KOTIAHO, Tapio

Date: _____
s/ MARTTILA, Seppo

(Legalization not required for recording but is prima facie evidence of execution under 35 U.S.C. §261)

Method and apparatus for mass spectrometric analysis

The present invention relates to a method according to the preamble of Claim 1 of examining a sample by means of mass spectrometry.

According to such a method, a solution containing the sample to be examined is first vaporised and, using a gas stream, the vaporised sample solution is then sprayed into the immediate vicinity of a corona discharge needle, where the sample to be examined is ionised. The charged particles are separated and, using electric and/or magnetic fields, conducted to a detector.

The present invention also relates to an apparatus according to the preamble of Claim 17, and to a use according to Claim 30.

Mass spectrometry is used in many fields of science, such as pharmaceutical research, genetics, environmental analyses and particle research. In mass spectrometry (hereinafter also abbreviated as "MS") material is examined on the basis of data about its mass, and with MS it is possible, among other things, to identify the compounds of a chemical sample and to determine their quantity ($< 10^{-11}$ M) in very small percentages, from complex sample matrices.

Typically, the sample to be examined is ionised in the ioniser of the mass spectrometer into a gaseous form and the gas-phase ions thus generated are separated on the basis of their mass/charge ratio (m/z) using electric and/or magnetic fields (mass analyser). The gas-phase ions are observed using a detector. The spectrum of the mass is established from a graph of the strength of the ionic current, which is generated by the detector, as a function of the m/z value of the ion.

The most commonly used method of ionising liquid samples is electrospray ionisation (ESI), where the sample, which is dissolved in a polar solvent, for example methanol, is introduced into a mass spectrometer through a thin needle-shaped capillary tube. When the capillary is exposed to high voltage (3-5 kV), a strong electrostatic field is formed at the tip of the capillary and, as a result, a charged aerosol is formed in the gaseous phase from the solution coming out of the capillary. The charged droplets of the aerosol emit gaseous-phase ions into the gaseous phase, and using a separate atmospheric pressure ion source they are collected in the mass analyser. In the ESI the ionisation takes place at normal pressure and it is suitable for examining even large molecules (MW > 100 kDa).

In the Atmospheric Pressure Chemical Ionization (APCI) method, the eluent is passed through a thin steel capillary which is installed inside a bigger steel tube. Between the tubes a spray gas is passed, causing the eluent to nebulize. The aerosol mist is led through a heated quartz tube, where the solvent and the compounds to be examined are vaporised. The vapour generated is ionised by means of a corona discharge electrode, to which a high voltage (3-5 kV) is connected. As a result of the electric discharge, the compound to be examined is ionised in the gaseous phase. The generated ions are collected for a mass analysis using an API dispatch. Unlike electric nebulizing, this method is suitable also for neutral molecules. In APCI, both polar and non-polar solvents can be used as the eluent, whereas in the ESI only polar solvents can be used.

The accompanying Figure 1 shows in more detail the principle of APCI ionisation. In the immediate vicinity of the tip of the electrode (needle), which is connected to a high potential, the strength of the electric field exceeds the corona discharge threshold of air, and the molecules (for instance N_2, O_2) in the air are ionised and changed into primary ions (N_2^+, O_2^+). The primary ions react with the solvent molecules (for instance H_2O, CH_3OH, NH_3) forming reagent ions (for instance H_3O^+, $CH_3OH_2^+$, NH_4^+). The reagent ions react with the sample molecules forming protonized ($[M+H^+]$) or deprotonized ($[M-H]^-$) molecules, which can be analyzed by mass spectrometry.

Depending on the type of the sample, the APCI ionisation is carried out either in a positive or negative mode. In the positive mode, the potential of the needle is higher than that of the curtain plate and the ionisation usually takes place by a proton transfer reaction. The proton transfer takes place according to Formula I (see below) if the proton affinity is higher than the proton affinity of the reagent gas:

$$XH^+ + M \rightarrow X + MH^+ \qquad (I)$$

In the negative mode, the potential of the needle is higher than that of the curtain plate and the ionisation takes place by deprotonation (II, see below) or electron transfer (III, see below). In the deprotonation, the reagent molecule has a higher proton affinity than the sample molecule. The electrons generated in the plasma in the electron transfer react with the sample molecules, which have a high electron affinity.

$$(X-H)^- + M \rightarrow X + (M-H)^- \qquad (II)$$

$$M + e^- \rightarrow M^- \qquad (III)$$

The most commonly used solvents are aqueous solutions of methanol (CH_3OH) or methylcyanide (CH_3CN). Protonation or deprotonation can be intensified by adding small amounts of additives to the solvent. For instance, ammonium acetate (CH_3COONH_4) can be used in positive mode, and acetic acid (CH_3COOH) and formic acid (HCOOH) in negative mode.

Because the compounds to be examined are brought into the gaseous phase by heating, the compound is fragmented more than in the ESI method. However, because the heating is very rapid, the compound is often not fragmented completely and a protonized or a deprotonized molecule is observed in the spectrum. The heating effect is separately optimized depending on the solvent/sample used. Usually, the temperature of the inner surface of the capillary is 100-150 °C. The generation of an effective spraying demands a rapid flow of the spray gas, approximately 2 l/min. In the APCI ionisation, the charge number of ions is usually one, which makes it possible to determine the molecular weight of the compound. On the basis of the fragments generated, information about the structure of the molecule can be achieved.

Feeding the analyte to the APCI ionisator takes place using a spray pump or a HPLC (High Performance Liquid Chromatography) pump. Using the pump, the flow can be adjusted even for very small quantities of liquid. In a conventional APCI, the flow of liquid is usually approximately 0.2-1 ml/min. By contrast, a gas flow is clearly higher than that, generally approximately 2 l/min. APCI is most suitable for ionisation of molecules of, at most, a few thousand Da.

A precondition for the corona to discharge is that the strength of the electric field exceeds the corona threshold value. In order to avoid an electrical breakdown, the electric field must be clearly non-homogeneous. A non-homogeneous electric field can be generated for instance by means of a sharp, needle-shaped electrode. In this case, the peak value of the electric field is located around the tip of the needle.

APCI is more suitable than ESI for analysing neutral compounds. In APCI, both polar and non-polar solvents can be used, whereas only polar solvents can be used in ESI. Moreover, high percentages of buffer agents or additives interfere with the ionisation clearly more in the ESI method than in the APCI. A disadvantage of APCI is that the sample speeds and flow speeds needed are significantly high. APCI is suitable only for flow speeds over 100 µl/min, and consequently, conventional APCI devices cannot be used for instance in microfluidic systems. Beyond that, the sensitivity of traditional APCI devices is not sufficient for small sample quantities.

Other disadvantages of known devices are relatively high manufacturing and operating costs, too. The latter costs include for instance substantial time spent for cleaning the devices.

The purpose of the present invention is to eliminate the disadvantages associated with the known technology and to generate a completely new way of examining samples in gas or liquid phase using mass spectrometry. In particular, the purpose of the present invention is to generate a working solution which is based on an APCI ion source, better suited to analysing small sample quantities than the devices used today. Another purpose of the present invention is to improve the sensitivity of APCI devices, and the heat transfer inside the vaporiser, too. Beyond that, a purpose of the present invention is to lower the manufacturing and the operating costs of the APCI devices.

The present invention is based on the idea that an APCI ioniser, suitable for analysing small sample quantities, is fabricated using micro mechanics. Miniaturized ESI solutions are already known, where flow channels for the sample solution and an injection tip used for ionising are machined in a monolithic, small glass plate. (Hereinafter, these devices are also called "ESI micro chips" or "μ-ESI devices"). Known technologies are described in US Patent Specifications No. 6,481,648 and 6,245,227. As with ESI technology in general, these miniaturized devices are suitable for ion-like compounds, but not for neutral and non-polar compounds, which cannot be ionised with ESI or for which the efficiency of ionisation is too weak.

The ESI liquid-feeding system is also described in the Published International Applications WO 00/41214, WO 01/53794 and WO 00/62039, and US Patent Specification No. 5,917,184. In these publications there are no suggestions that the described feeding equipments would be used for vaporising the sample, in which case the equipment would be suitable for APCI. In the application WO 01/53794 there is a reference to heating, but in the known equipment heating is used for pumping of the sample solution. The solution is based on thermal expansion of the sample or bubble formation, and the sample is not vaporised.

An unsolved disadvantage of using known ESI micro chips as miniaturized devices is that the high voltage electric field remains concentrated at the tip of the μ-ESI device, i.e. the exit port of the microfluidic system, which destroys this tip rapidly, which in turn limits the

operating life of the μ-ESI and prevents generation of proper and stable analyses. In addition, the oxidation and the reduction reactions taking place at the tip of the ESI sprayer lead to clogging of the tip and formation of bubbles.

Associated with the present invention it has been found that a miniaturization of the process is considerably more appropriate for the APCI technique ioniser than for the ESI ioniser mentioned above. According to the present invention, parts of the device which are typical to the APCI ioniser, at least the flow channel networks for gases and liquid, and the heater of the vaporiser, are included in a monolithic structure, where the flow channels are dimensioned so that the liquid flow is less than approximately 100 μl/min.

In the μ-APCI method, because the high voltage electric field is concentrated at the tip of the corona discharge needle and not at the exit point of the microfluidic system, this exit point is not vulnerable to destruction. Furthermore, at the same time, it is possible to carry out a proper and stable analysis.

By using a device according to the present invention even small sample quantities can be vaporised and they can be ionised in a corona discharge zone, for instance a corona discharge needle, which forms part of the microchip or which is arranged in linkage with the microchip.

More specifically, the method according to the present invention is mainly characterized by what is stated in the characterization part of Claim 1.

The device according to the present invention is, in turn, characterized by what is stated in the characterizing part of Claim 17.

The use according to the present invention is specified in Claim 30.

Considerable advantages can be achieved with the solution according to the present invention. Thus, the manufacturing process of the device is simple enough to yield the required result.

The present invention generates a new interface between any microanalytic system of a microfluidistic type, or any other type, and a mass spectrometer. The device can be used in particular for small flow volumes (less than 5 μl/min), but it is also suitable for flow

volumes of as small as approximately 100 μL. The most important fields of application of the present invention are bioanalyses, pharmacological analyses, drug analyses, environmental toxins analyses, food analyses, clinical analyses and diagnostics. The method and the device are especially suitable for cases in which very sensitive analysis techniques are needed, or in which the quantity of the sample available is very small (less than 1 μL).

The present invention can be applied to analysing many kinds of compounds. It is suitable for both polar and non-polar compounds, and for neutral compounds and ionic compounds, too. In principle, it is possible to analyse all compounds which comprise a functional point, such as a functional group that can be protonized. Examples of especially interesting applications are slightly polar compounds, classified as non-polar, in which the percentages of these in the samples are very low. Examples of these are different steroids, such as neurosteroids, which comprise at least one hydroxy group or, correspondingly, ketone group. The quantities of such compounds in biological samples are in the range of 10-100 picograms per millilitre. In addition, the present invention can also be used for analysing alkaline nitrogen compounds, which generally form the main part of, for instance, all pharmacologically active agents.

Consequently, the solution can be used for analysing both liquid and gas phase samples. The eluent used for dissolving the sample can be either a polar and/or a non-polar solvent.

The micro-APCI technique according to the present invention is especially usable for compounds which can be vaporised, especially at normal atmospheric pressure, and the molar masses of which are usually approximately 50-2500 Da, preferably at most 2000 Da, most suitably at most 1000 Da.

Compared to the μ-ESI technique, the μ-APCI generates a better sensitivity for analyses of polar and neutral compounds. Non-polar eluents can be used in the analyses, and, if desired, even gas phase samples can be analysed.

Compared to the conventional APCI technique, considerable advantages, too, are achieved with the present invention. Accordingly, in the present invention, the flow rates range from nanolitres to a few dozen microlitres, whereas the conventional APCI is suitable only for flow rates which are higher than 100 μl/min. The present invention can be used for analyzing smaller sample volumes and the device has a significantly better sensitivity than

the conventional APCI. In addition, the heat transfer and the vaporisation have been improved.

The costs of production of the μ-APCI are significantly lower than of the conventional APCI. Consequently, the present invention makes it possible, in principle, to manufacture disposable vaporisation/ionisation devices, in which case a spent device, after becoming dirty, can be replaced with a totally new device. This significantly cuts down the time needed for cleaning the MS device.

In the following, the invention will be examined and explained in more detail, with the help of the accompanying drawings:
Figure 1 shows a block diagram of the parts of a mass spectrometer device,
Figure 2 shows the principle of the basic solution of APCI ionisation,
Figure 3 shows the structures of two alternative embodiments of the device according to the present invention, simplified and depicted from above and from the side, respectively, whereby Figures 3a and 3b show the structure of the horizontal micro-APCI ion source and, correspondingly, Figures 3c and 3d the structure of the vertical ion source,
Figures 4a and 4b show the chip configurations of the structures shown in Figure 3a, as versions modified with a planar needle,
Figures 5a and 5b show a microchip equipped with a three-dimensional needle, simplified and depicted from above and from the side, respectively,
Figures 6a and 6b show an alternative feeding system depicted from above, and details of the system, and
Figure 7 shows the application according to Figures 6a and 6b depicted from the side.

In known technology, a micro-electromechanical system (MEMS/MST) generally refers to a system where micromechanical and microelectronic structures have been integrated on the same microchip (typical size range 1 mm^2 -10 cm^2). It is known that micromechanical structures (range of dimensions 0.1 μm-1 mm) can be manufactured by etching a substrate wafer (bulk-micromechanics) or by patterning thin films built up on a substrate wafer surface (surface micromechanics). Substrate materials generally used in micromechanics are silicon, glass, GaAs, quartz and plastics. For instance, silicon dioxide, silicon nitride, amorphous/polycrystalline silicon, metals and polymers are used as thin films (thickness range 1 nm-1 mm).

In the present invention, a micronized structure is called simply "a micromechanical structure". By this is meant a unit (size approximately 1 mm^2-10 cm^2) which is fabricated on a substrate wafer/wafers and which comprises structures, such as channels and resistors, which are essential to the operation of the component.

In the method according to the present invention a solution comprising the sample to be examined is vaporised in a vaporiser in the form of a micromechanical device. The vaporiser comprises a monolithic block in which at least flow channels for the sample solution have been formed, as well as flow channels for a possible carrier gas, plus a heater for the sample solution. The vaporised sample solution generated is sprayed, using a gas flow, into a corona discharge zone, where the sample to be examined is ionised using a corona discharge to produce gas phase ions, after which the ions are separated and led to a detector, using a method, for instance with electrical and/or magnetic fields, which is known *per se*.

In this invention, a "monolithic" block means a block which comprises only one single part or has been formed of two or more parts, which, using a bonding-technique, have been joined together to form one single block so firmly that the parts can no longer be detached from each other without substantially breaking the parts.

According to a preferred embodiment of the present invention a micromechanical structure is used, one which comprises a substrate wafer or a stack of several connected discs, in which flow channel networks for gases and liquid as well as a heater for vaporising the sample solution have been constructed. In this case, the monolithic block is formed of two or more blocks which have been joined to each other. A single block such as this can comprise smaller blocks all of which are identical or, alternatively, different, and made of, for instance, glass or silicon. Consequently, the flow channels for gases and liquid together with their inlet openings and heater for the vaporiser can be constructed in the same part or in different parts which are placed against each other. The block can, for instance, comprise a glass plate in which the flow channel systems for gases and liquid have been formed, as well as a silicon wafer in which a heater used for vaporising the sample solution is constructed. The structure can be reversed, too.

The entire device can also be made of one material, for example glass. A preferable embodiment of the present invention comprises a device which can be made using either wet or plasma processing (DRIE, deep reactive ion etching), or the channel systems can be made by using sand blasting, too. The masking material can be for instance polycrystalline silicon, amorphous silicon, chromium, nickel or SU-8 epoxy resist, which are built up by

sputtering, vaporising, electrochemical deposition or spin-coating. The through holes can be carried out by sand blasting or drilling, too.

SU-8 masking is described in more detail for instance at the address http://www.microchem.com/products/su_eight.htm

According to the present invention, the flow channel networks have been dimensioned so that the flow of liquid through them is less than 100 µl/min, most suitably at most approximately 50 µl/min, especially at most approximately 10 µl/min. Generally, the sizes of the channels vary depending on whether the substance flowing through them is gas or liquid. A typical size of a gas-feeding channel (the width or the depth of the cross-section) is approximately 10-1000 µm, especially approximately 20-500 µm, and the corresponding size of the liquid flow channel is approximately 5-500 µm, especially approximately 10-250 µm, though these are not limiting dimensions. The depth of the channels is usually smaller than the height, in which case the depth is usually less than 200 µm. If the cross-section of the channels is circular, their diameter is typically within the general range mentioned above.

The nebulizing gas can be fed either in the direction of the sample or essentially perpendicular to the flow direction of the sample, as is described in more detail below with reference to Figures 6a, 6b and 7. The gas flow used in the injection is brought essentially perpendicular to the flow direction of the sample. In both applications the gas flow is fed into the device preferably in the direction of the liquid before the inlet opening of the liquid. When the gas flow is fed in perpendicular direction, through one inlet opening, the gas flow is efficiently distributed around the liquid flow comprising the sample, and the gas is extremely homogeneously mixed with the solution.

According to one embodiment, the vaporiser according the present invention comprises both a vaporising and a corona discharge zone which have been integrated to create one single micromechanical structure. However, it is possible to fabricate the corona discharge zone as a separate part of the device.

The sample solution vaporised in the device is ionised by a corona discharge in the presence of air, according to the APCI method. Most suitably, this is carried out at normal atmospheric pressure. In the vaporisation the sample is heated so much that the material to be examined is sufficiently well vaporising while the compound is still essentially in an

undegraded form. Generally the sample is heated to its boiling point, which, depending on the material to be examined, varies between approximately 30 and 350 °C. The normal vaporisation temperature is approximately 200-300 °C, and at least 20 mole-%, especially at least 40 mole-%, preferably 50-100 mole-% of the sample to be examined is vaporised. Of the vaporised compound/material 5-100 mole-%, preferably at least approximately 10 mole-%, especially at least 20 mole-% (and even 95 mole-%) is in the gaseous phase in an undegraded form.

Typically, the corona discharge zone comprises a needle-shaped electrode, which is connected to a potential which is so high in relation to the curtain plate of the mass spectrometer that the electric field strength, at least in the immediate vicinity of the tip of the electrode, exceeds the corona discharge threshold of air. The potential of the needle-shaped electrode in relation to the curtain plate is, for instance, at least 1 kV and the maximum electric field near the tip of the electrode is approximately 50 kV/mm.

Figures 3a-3d, attached, show two embodiments of the present invention. As the figures show, the device according to the present invention can, for example, be fabricated following two different configurations, namely horizontal (Figures 3a and 3b) or vertical (Figures 3c and 3d). In the horizontal solution, the chip (and, accordingly, the needle and the flow exit port) is perpendicular to the curtain plate of the mass spectrometer, and in the vertical solution the chip is parallel to it.

Figures 3a and 3b show the structure of a horizontal μ-APCI ion source. As the lateral view shows, the device comprises a glass plate (1), on which a silicon wafer (2) has been arranged. Into the silicon wafer (2), feeding holes for liquid (3) and, correspondingly, for gas (4) have been machined. The silicon wafer has been equipped with a mixing zone (5), too, to which the feeding holes (3 and 4) for liquid and gas, respectively, have been connected through the feeding tube systems (6 and 7). The mixing zone comprises, for instance, a capillary tube, which has been arranged in the silicon wafer and which has been equipped with a heating resistance (8). In order to vaporise the liquid, this heating resistance can be used to heat the liquid and gas flows which are fed into the capillary and mixed in it. Connected to the heating resistance (8), are electric wires (9), which at one end, i.e. at the glass plate surface, are equipped with contact electrodes (10), to which an electric source can be connected.

In the devices in Figures 3a and 3b an electrode needle (11) which produces the corona discharge, has been arranged parallel to the glass plate (1) and the capillary tube (5). The

electrode needle (11) is connected through electric wires to the contact electrodes (13), too. At the exit end of the capillary tube there is an orifice (12) from which the ionised gas spray, coming from the electrode needle (11) can be discharged and led to a mass spectrometer to be analysed.

The devices according to Figures 3c and 3d are basically of the same structure as the devices described in Figures 3a and 3b. Accordingly, there is a glass plate (21), and a silicon wafer (22) on top of it. In this case, however, the feeding holes (23 and 24), for liquid and gas, respectively have been arranged in the glass plate. In the silicon wafer, a mixing zone (25) has been machined to which gas and, correspondingly, liquid can be led through their respective feeding tube systems (26 and 27). The device is equipped with a heater (28), including its electric wires (29) and contact electrodes (30), which surround the mixing zone (capillary no. 25). The electrode needle (31) is arranged horizontally towards the mixing zone orifice (32).

The ionisers shown in Figures 3a-3d can be fabricated for instance by etching the channel networks (5-7; 25) into the silicon disc, using anisotropic wet etching. The metallic planar needle (11, 31) and the heater (8, 28) are patterned in the glass plate, which is finally attached to the silicon wafer using anodic bonding.

The advantages of this solution are easiness of etching and bonding.

Besides anodic bonding, the joining can be carried out for instance by glass frit bonding, thermo-compression bonding or glue bonding, in which case conventional polymer-based adhesives can be used as intermediate agents. Typical examples are epoxy-polymers, negative and positive resists, polyimides, PMMA, silicones and fluoro-elastomers.

Generally, the polymer glue seam is not hermetic and it does not withstand high temperatures, but on the other hand the bonding can be carried out at low temperatures (depending on the polymer, even at below 100 °C) and for a large variety of materials, which makes it an attractive alternative in, for instance, CMOS processes. The glue bonding method comprises careful washing and drying of the discs/chips to be connected, spreading of adhesion promoter, spinning/spraying of polymer (thickness for instance 1-20 μm) on both or one of the surfaces to be connected, prebake-heat treatment (for instance 60-100 °C, 10 min), placing the discs/chips under compression in a vacuum chamber, and the hardbake-heat treatment (for instance at 100-300 °C, 5 min).

The present invention can also be constructed entirely of glass, which is a solution that further improves the thermal and electrical properties of the device.

Depending on the testing device, the width of the gas feeding channels of the fabricated testing devices has been 270, 320 or 370 μm. The liquid feeding channel, in turn, has been 120, 130 or 140 μm, and the width of the mixing/heating channel 1.27 mm. The length of the feeding hole side has been 670 μm in the horizontal model and in the vertical model almost 2 mm, because of the glass drilling allowance. The depth of the channels has varied between 85 μm and 190 μm, because of the anisotropy of the etching (narrowness of the channels).

The planar heater and needle can be patterned in the metal layer which is sputtered, vaporised or built up in some other way on the glass plate (1 and 21, respectively). The metal can be a precious metal, such as platinum, or a base metal which has a high electrical and/or thermal conductivity, such as aluminium, and which is inert enough for the sample to be examined. The thickness of the metal layer to be built up can be freely chosen; in the testing solution a thickness of 300 nm was chosen, in which case the resistance at room temperature was approximately 85-90 Ω for the horizontal chips, and for the vertical chips approximately 43 Ω.

The length of the electrode needle is usually approximately 0.5-10 mm, preferably approximately 1-6 mm. The testing devices were fabricated using a needle length of 2 or 3 mm for the horizontal model, and 2 or 2.5 mm for the vertical model.

At the points of the contact electrodes, the silicon can be made thinner by etching, and thereby make the electrodes emerge from the silicon-glass interface. It is not advantageous to etch through the silicon at these points because the physical strength of the wafer (with regard to the bonding) may suffer. A three-dimensional microneedle eliminates this problem, because, in this case, there would be ample volumes of ionisable gas in the immediate vicinity of the tip of the needle. Due to the miniaturization of the ion source, analysing small quantities of samples (flow magnitude μl/min) is easier and the measuring sensitivity improves.

In the following, a practical example of the process of manufacturing the present ionisers is described:

A 380 μm thick n-type (100) wafer, polished on both sides, was chosen as the silicon

substrate of the chip. High- resistance (> 500 Ωcm) wafers were used to fabricate the prototypes, in order to reduce the leakage of current from the heater. A 0.5 mm thick glass wafer of type Corning Pyrex 7740, which can be anodically bonded to the silicon, was used as the chip cap.

The manufacturing process started with RCA-washing of the silicon wafers. Organic contamination was removed by means of RCA-1-washing and metallic contamination by RCA-2-washing. A HF-dip was carried out between the washings. After the washings, a thermal oxide of approximately 600 nm was built up on the silicon wafers, using a wet oxidisation process. A HMDS layer was vaporised onto the oxidised wafers to improve the adhesion of the resist, after which a 1.4 μm photoresist (AZ 5214) was spun onto the wafers. After the prebake, the resist was exposed through mask no. 1. After the development of the layer and the hardbake, the oxide was removed by etching from the channel areas. After the oxide etching, the resist was removed with acetone and isopropanol.

When the channel areas had been patterned on the front side of the silicon wafer, the lead-ins were patterned on the reverse side of the wafer. The resisting of this reverse side was carried out in the same way as described above. The Electronic Visions AL-6 device with microscopes above and under the wafer was used as a locator for two-sided registering. After the registering and the exposure, the development, hardbake, possible resisting of the front side, oxide etching and resist removal were carried out once again.

The etching of the wafers was carried out in a 20 m-% TMAH solution at 80 °C. Because of the water-circulated heating and the vapour barrier of the etching vessel, the temperature of the entire etching solution was kept constant throughout the process. Moreover, the wearing of the etcher by vaporising was minimal. The etching time was 9 hours. When the etching was completed, the wafers were rinsed very thoroughly in bubbling DI water to ensure that the TMAH residues would leave no film on the surface of the wafers.

Pyrex glass wafers, the processing of which started with acetone and isopropanol washing, were chosen as the initial material for the glass plates. After careful drying, an aluminium layer of approximately 300 nm was sputtered onto the glass wafer in an Oxford sputter. Following the sputtering, a photoresist, which was applied onto the aluminium layer, was patterned with the mask no. 3, using photolithography. Excess aluminium was removed in an aluminium etcher containing phosphoric acid. After that, the inlet holes of the vertical model chip were drilled in the glass. For the drilling, the glass wafer was resisted on both sides and glued, using resist, to the silicon wafer so that the bonded side was uppermost. A

0.8 mm diamond-coated hard metal tip and DI-water cooling were used for the drilling. After the drilling, the wafers were separated from each other using acetone washing in an ultrasonic basin.

The last stage of operation was to attach the processed silicon and glass wafers to each other using anodic bonding. A bonder type comprising a bonding chamber, a control unit and a mechanical vacuum pump was used for the bonding. The bonding chamber comprised heaters above and under the wafer, plus altogether four probes for measuring the temperature, a pressure probe and a press operated by compressed air. The control unit can be used to regulate the temperature of the chamber, the pressure, the compression and the voltage/current across the package of wafers.

After bonding, the sawing of the chips was carried out. It was possible to reveal the contact pads at the interface after the sawing by bending away the thin silicon strip on top of them. Finally, the fluidic connectors were glued to the chips using epoxy glue.

The inlet connectors which enable connecting of the micro hoses were glued to the chips. Using commercial inlet connectors, it was possible to attach the capillaries to the chips by screwing them on, resulting in a tight and easily releasable connection. The outside diameter of the liquid and the gas capillary was 360 μm and the inside diameter 150 μm.

It was decided that the operation of the micro channel networks would be studied using a video camera attached to a microscope. A nitrogen flow was connected to the heated chip, and, using an injection pump, the test sample was fed into the micro channel network. The test sample used was fluoresin, which was dissolved in methanol and, using a xenon lamp, tuned to be gleaming. During the measuring, the flow rate of the liquid was maintained at a few μl/min. This method can be employed to observe how the micro channel network operated under regimes of different gas and liquid flow rates. It was found that the frequency at which the micro droplets – which formed at the end of the liquid channel – detached largely depended on the flow rate of the gas. During the measuring, the feeding pressure of the gas used was several bars at most, but it was difficult to estimate the actual flow rate. If the heating was switched on, the droplets were rapidly vaporised from the end of the liquid channel.

To connect the horizontal and the vertical model chips to the mass spectrometer, supports made of Teflon were fabricated for both them.

For the test measurements, the chip was connected to a API 300 series mass spectrometer, manufactured by PE Sciex Instruments.

The mass spectrometer's own 8 kV source was used as the high voltage source. Batteries (12 V or 24 V) were used as the power source for the heater. A multimeter was used to measure the current through the heater. A separate flow pump, which could be used to regulate the flow at a µl/min-level, was used for the pumping of the sample solution. Depending on the gas used, either the mass spectrometer's own feeding system or a separate gas feeding system was used to feed the nebulizing gas.

Midazolam ($C_{18}H_{13}ClFN_3$, M = 325.8) and pyridin (C_5H_5N, M = 79.1), dissolved in methanol, were used as test solutions. Midazolan is a drug that has a very high proton affinity. Pyridin, too, has a high proton affinity and also a low boiling point (115 °C).

The measurements were carried out in a so called "heated nebulizer" mode, and it was decided that they would begin using the mass spectrometer's own corona discharge needle. To begin with, air was used as the nebulizing gas because it was possible to regulate its flow with the controlling programme of the mass spectrometer. The testing of the horizontal model was started using only solvent (methanol). The basic parameters used are shown below:

- Flow rate of sample: 1 µl/min
- Flow rate of nebulizing gas: 1.04 l/min (theoretical set value)
- Flow rate of curtain gas: 0.95 l/min
- Corona discharge current: 0.1 µA
- Voltage of heater: 12/24 V (corresponds to temperature of horizontal model, approximately 70 °C/195 °C)
- Other values are default values of measuring programme

A clear signal was obtained when only methanol was used. Subsequently, pyridine was tested using a concentration of 10 µg/ml, and a weak signal was obtained. A better signal was obtained with 1 mg/ml of midazolam. When nitrogen was chosen as the nebulizing gas, the background disturbance signals were significantly decreased.

However, the nebulizing gas and the curtain gas flows did not have any significant effect. Only very low (nebula: 0.03-0.41 l/min, curtain: 0-0.44 l/min) and high (nebula: 1.49-1.58

l/min, curtain: 1.58-1.84 l/min) values had an effect. At low curtain gas flows, the background noise increased and with high flows the sample intensity decreased. The effect of the nebulizing gas flow varied according to the sample flow rate. At high sample flow rates (10-100 µl/min), reduction of the nebulizing gas did not have any significant effect on the peak intensity. At low flow rates (<10 µl/min) the intensity improved with growing nebulizing gas flow.

The temperature is chosen so that the examined material is vaporized well enough without the compound being degraded too much.

To improve the operation of the device, the silicon substrate can be electrically isolated from the electrode needle. This can be done for instance by building up an insulating layer of oxide or nitride, using PECVD, on the top of the metal pattern on the glass wafer. It is also possible to pattern a planar needle on the glass wafer after the bonding of the wafer. The chip can be totally made of insulating material, too.

Regarding the simplicity of the manufacturing process, a significant advantage can be achieved with planarity of the micro needle; a three-dimensional needle is more difficult to fabricate. Figure 4 shows two modified chip configurations (glass 31 and 41, silicon 32 and 42) with a planar needle (33 and 43). The parts of the device are the same as in Figure 3a. As Figure 4 shows, the needle can be situated directly in front of the exit hole of the vaporisation products, parallel to the capillary, or it can be directed diagonally from the side to the front of the exit hole. A three-dimensional micro needle, 53 (see Figure 5, device parts otherwise the same as in Figure 3a), built on the glass and silicon wafer, 51 and 52 respectively, could be fabricated using for instance needles which are flexible due to membrane stresses, structures which are based on metal-coated polymers, needles based on bonded metal wires or micromechanically upliftable solutions, or electrochemically sharpened metal wire, for instance platinum wire.

Figures 6a, 6b and 7 show an alternative solution in which the nebulizing gas, which is usually inactive (or inert), such as nitrogen, comes from the top of the chip (101) through a feeding nozzle such as nanogate (102). Consequently, the gas is fed at least substantially perpendicular to the sample and not in the sample direction, as in the embodiment described above.

The thin tube marked with reference number (109) in Figures 6a, 6b and 7 is the connecting capillary tube coming from the liquid chromatograph (LC).

The inlets (103) for liquid and (104) for gas, respectively, have been processed in the silicon or glass wafer (101) which is on the glass plate (114). To get the capillary end positioned, wedge-shaped guides (113), which form a tapering hole, have been processed in the wafer. The wafer has been equipped with a mixing zone (105), too, to which the feeding holes (103 and 104) for liquid and gas, respectively, have been connected through the flow channels (106 and 107) (cf. also the arrows).

As the figure shows, the gas coming from the gas inlet (104) circulates, as shown by the arrows, around the end the capillary tube before it is mixed with the liquid flow in the mixing zone (105).

The wafer is equipped with heating resistors (108), which can be used to heat the liquid flow which is fed through the capillary and in which the nebulizing gas flow is mixed in the mixing zone (105), in order to vaporize the liquid. The heating resistor connectors are numbered (110) and as the figure shows the foreparts of the heating resistors are made wider in order to decrease the flow resistance, and they are made narrow only near the mixing zone of gas and liquid, where they form the actual heating zone (111) and act as heating resistors.

The solution according to Figures 6a, 6b and 7 is based on the same basic principle as the devices described above, but the structure according to that solution is simpler and the dead volumes are minimized. The feed nozzle of the gas is located in the direction of the liquid flow, upstream, which means that the gas is brought into the device (in the direction of the liquid flow) before the inlet opening of the liquid. Because the nebulizing gas is brought in from only one nozzle and one opening, from which it is distributed to both sides/around of the sample flow, it is easy to use this solution to generate a homogeneous mixture.

Claims:

1. A method of examining a sample by means of mass spectrometry, according to which method

- the solution comprising the sample to be examined is vaporised in a vaporiser;
- the vaporised sample solution is sprayed, using a gas flow, into a corona discharge zone, where the sample to be examined is ionised using a corona discharge to generate gas phase ions; and
- the ions are separated and directed to a detector,

c h a r a c t e r i z e d by

- using a vaporiser which is fabricated as a micromechanical structure.

2. A method according to Claim 1, c h a r a c t e r i z e d in that a vaporiser is used which comprises flow channel networks for the solution and for the carrier gas possibly used for the feeding of the solution, as well as a heater of the vaporiser, which are all included in a monolithic structure.

3. A method according to Claim 2, c h a r a c t e r i z e d in that the flow channel networks are dimensioned so that the volume of the liquid flow passing through them is less than 100 µl/min, most suitably less than 10 µl/min.

4. A method according to Claim 2 or 3, c h a r a c t e r i z e d in that a vaporiser is used which comprises a vaporising zone and a corona discharge zone, which are integrated into a single micromechanical structure.

5. A method according to any of the preceding claims, c h a r a c t e r i z e d in that a micromechanical structure is used which comprises flow channel networks designed for one or more wafers, and a heater.

6. A method according to Claim 5, c h a r a c t e r i z e d in that a structure is used which comprises

- a substrate wafer in which flow channel networks for gases and liquids are formed, and
- a cover wafer, attached to the substrate wafer in which a heater for vaporising the sample solution, is patterned.

7. A method according to any of the preceding claims, c h a r a c t e r i z e d in that the vaporised sample solution is ionised with a corona discharge in the presence of air, at normal atmospheric pressure.

8. A method according to any of the preceding claims, c h a r a c t e r i z e d in that the corona discharge zone comprises a needle-shaped electrode, which is connected to a voltage which is so high in relation to the curtain plate of the mass spectrometer that the electric field strength, at least in the immediate vicinity of the tip, exceeds the corona discharge threshold of air.

9. A method according to Claim 8, c h a r a c t e r i z e d in that the potential of the needle-shaped electrode in relation to the curtain plate is at least 1 kV, and the maximum electric field strength near the tip of the electrode is approximately 50 kV/mm.

10. A method according to any of the preceding claims, c h a r a c t e r i z e d in that polar compounds, non-polar compounds, neutral compounds or ionic compounds are examined, and the sample to be examined is dissolved in a polar or non-polar solvent, used as the eluent, to generate the sample solution.

11. A method according to Claim 10, c h a r a c t e r i z e d in that compounds are examined, the molar masses of which are at most 2000 Da, most suitably at most 1000 Da.

12. A method according to any of the preceding claims, c h a r a c t e r i z e d in that the flow of liquid of the sample to be examined is set at a value which is lower than approximately 10 µl/min, and the flow of the carrier gas used for feeding the sample is set at a value which is at least approximately 50 µl/min.

13. A method according to any of the preceding claims, c h a r a c t e r i z e d in that the sample is ionised using the Atmospheric Pressure Chemical Ionization (APCI) method.

14. A method according to any of the preceding claims, c h a r a c t e r i z e d in that the gas flow used for the injection is brought in essentially perpendicular to the flow direction of the sample.

15. A method according to any of the preceding claims, c h a r a c t e r i z e d in that the gas flow is fed into the device in the flow direction of the liquid and before the feed opening of the liquid.

16. A method according to Claim 14 or 15, c h a r a c t e r i z e d in that the gas flow is fed through one feed opening, in order to distribute the gas flow around the liquid flow comprising sample, and, as a result, a homogeneous mixture is achieved.

17. An apparatus for examining a sample by means of mass spectrometry, comprising

- a vaporiser for vaporising the solution comprising the sample to be examined,
- a corona discharge device, connected to the vaporiser, in which the sample to be examined is ionised according to the Atmospheric Pressure Chemical Ionization (APCI) method, to generate charged particles,
- a detector, connected to the corona discharge device, to detect charged particles, and
- means for directing the charged particles, using electric and/or magnetic fields, from the corona discharge device to a detector,

c h a r a c t e r i z e d in that

- the vaporiser is fabricated as a micromechanical structure.

18. An apparatus according to Claim 17, c h a r a c t e r i z e d in that the vaporiser comprises flow channel networks for the solution and for carrier gas possibly used for feeding the solution, and a heater of the vaporiser, which are all included in a monolithic structure.

19. An apparatus according to Claim 18, c h a r a c t e r i z e d in that the flow channel networks are dimensioned so that the volume of the liquid flow passing through them is less than 100 µl/min, most suitably less than 10 µl/min.

20. An apparatus according to Claim 18 or 19, c h a r a c t e r i z e d in that the vaporiser comprises a vaporising zone and a corona discharge zone, which are integrated into a single micromechanical structure to form a combined vaporiser and corona discharge device.

21. An apparatus according to any of the Claims 17-20, c h a r a c t e r i z e d in that it comprises a monolithic block which is formed of two or more parts which are connected to each other.

22. An apparatus according to Claim 21, c h a r a c t e r i z e d in that the block comprises a

silicon wafer in which flow channel networks for gases and liquid are formed, and a glass plate in which a heater for vaporising the sample solution is formed.

23. An apparatus according to Claim 21, c h a r a c t e r i z e d in that the block comprises a glass plate in which flow channel networks for gases and liquid are formed, and a silicon wafer in which a heater for vaporising the sample solution is formed.

24. An apparatus according to any of the Claims 17-23, c h a r a c t e r i z e d in that the corona discharge device comprises a needle-shaped electrode, which is connected to a potential which is so high in relation to the curtain plate of the mass spectrometer that the electric field strength, at least in the immediate vicinity of the tip of the electrode, exceeds the corona discharge threshold of air.

25. An apparatus according to Claim 24, c h a r a c t e r i z e d in that the potential of the needle-shaped electrode in relation to the curtain plate can be set at a value which is at least 1 kV, and the maximum strength of the electric field near the tip of the electrode can be set at approximately 50 kV/mm, at least.

26. An apparatus according to any of Claims 17-25, c h a r a c t e r i z e d in that it is fabricated entirely as a glass structure.

27. An apparatus according to any of Claims 17-26, c h a r a c t e r i z e d in that the flow channel system of the carrier gas used for feeding the solution is connected to a feed nozzle of the gas, which nozzle is located upstream in the flow direction of the solution and through which gas can be fed into the device essentially perpendicular to the flow direction of the solution.

28. A device according to Claim 27, c h a r a c t e r i z e d in that the gas flow fed through the feed opening can be distributed around the flow channel system of the solution in order to achieve a homogeneous mixture.

29. A device according to any of the Claims 17-28, c h a r a c t e r i z e d in that the heater comprises heating resistors, the foreparts of which are made wide in order to decrease the flow resistance and which are made narrow only near the mixing zone of gas and liquid, where they act as heating resistors and form the actual heating zone.

30. Use of a vaporiser, fabricated as a micromechanical device, to generate a vaporised sample which is fed to be ionised according to the Atmospheric Pressure Chemical

Ionization (APCI) method.

31. Use according to Claim 30, c h a r a c t e r i z e d in that a vaporiser is used, which comprises a monolithic block, in which at least the carrier channel networks for the sample to be examined and for the carrier gas possibly used for feeding the sample, as well as the heater for vaporising the sample are formed, in which case the flow channel networks are dimensioned so that the flow volume passing through them is less than 100 µl/min.

32. Use according to Claim 31, c h a r a c t e r i z e d in that the vaporiser is used for examining a sample, the molar mass of which is at most approximately 2000 Da.

(57) Abstract:

A method and an apparatus for examining a sample by means of mass spectrometry. According to the method, the solution comprising the sample to be examined is vaporised in a vaporiser, the vaporised sample solution is sprayed, using a gas flow, into a corona discharge zone, where the examined sample is ionised according to the APCI method, using a corona discharge, to generate gas phase ions, and the ions are separated and directed to a detector. According to the present invention, a vaporiser is used, which is fabricated as a micromechanical structure which comprises the flow channels for the solution and for the carrier gas possibly used for feeding the solution, as well as the heater of the vaporiser, and which are all included in a monolithic structure. The solution is especially suitable for cases in which a very sensitive analysing technique is needed, or in which the available sample quantity is very small (less than 1 μL).

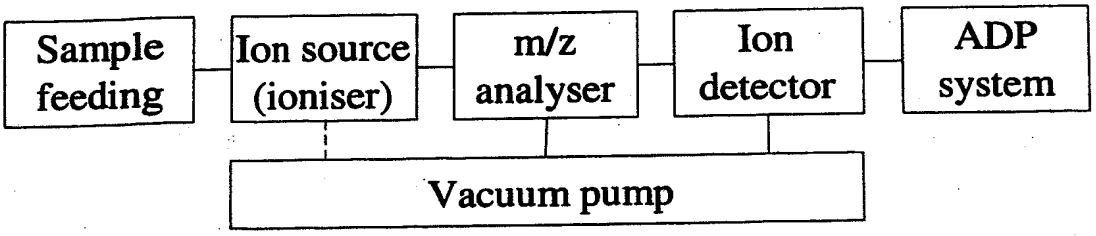
Sample feeding
Ion source (ioniser)
m/z analyser
Ion detector
ADP system
Vacuum pump

Fig. 1

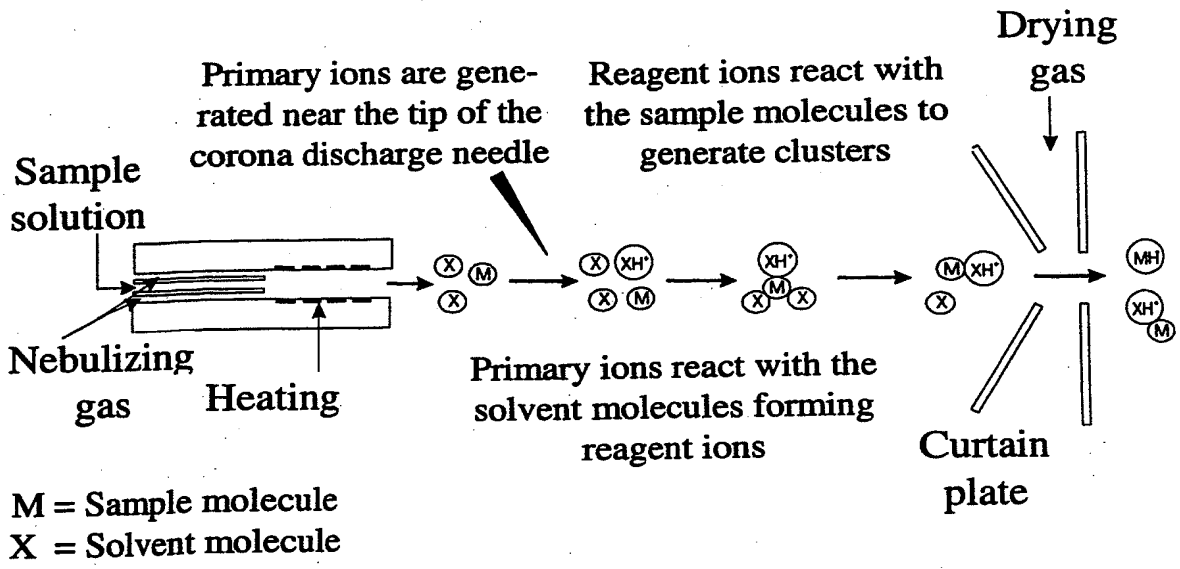
Drying gas
Primary ions are generated near the tip of the corona discharge needle
Reagent ions react with the sample molecules to generate clusters
Sample solution
Nebulizing gas
Heating
Primary ions react with the solvent molecules forming reagent ions
Curtain plate
M = Sample molecule
X = Solvent molecule

Fig. 2

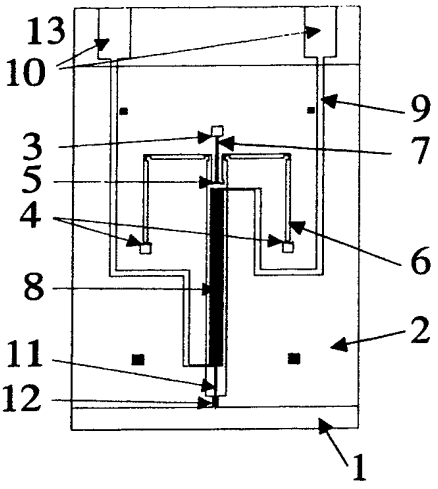

Fig. 3a

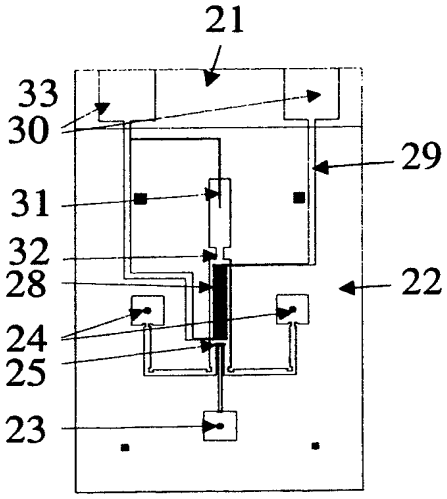

Fig. 3c

Fig. 3b

Fig. 3d

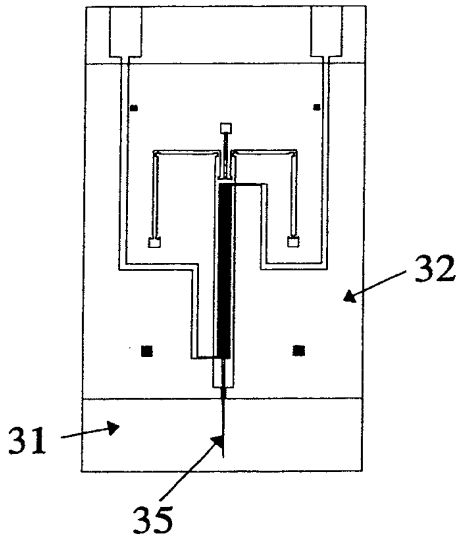

Fig. 4a

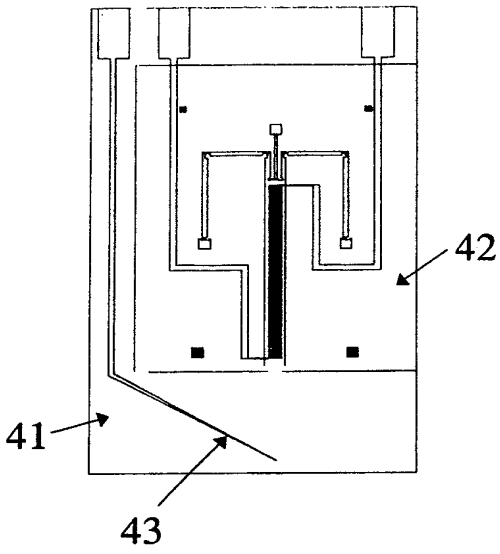

Fig. 4b

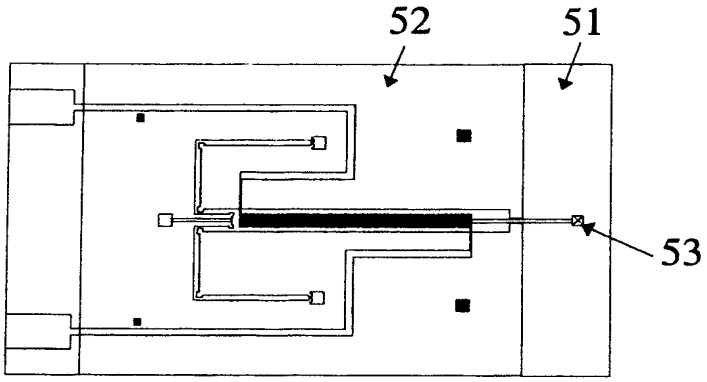

Fig. 5a

Fig. 5b

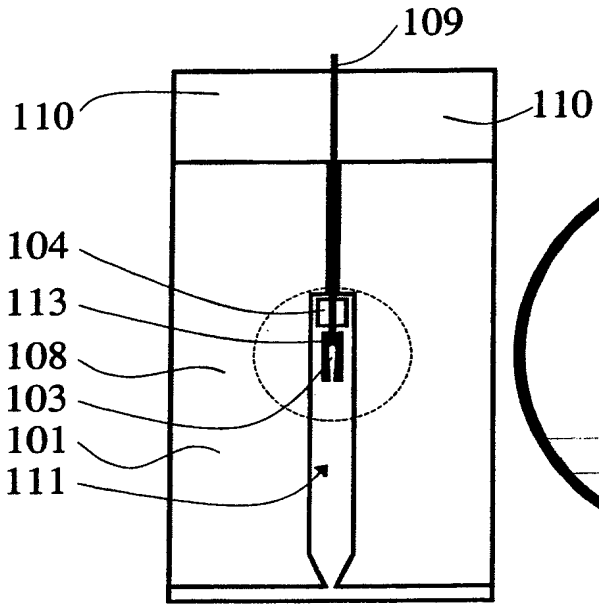

Fig. 6a

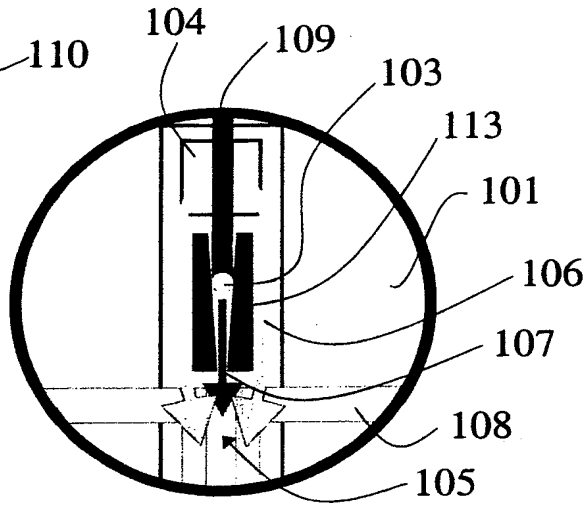

Fig. 6b

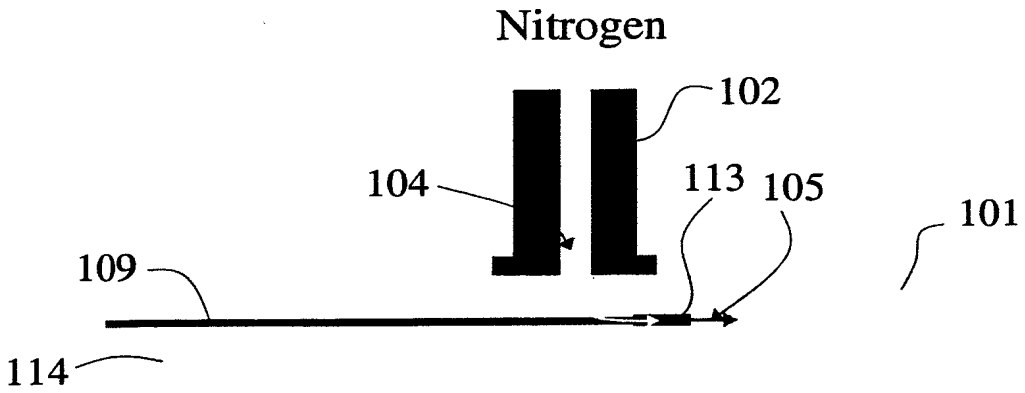

Fig. 7

EXHIBIT B

Translation from Finnish

LICENTIA

Licentia Ltd
Tukholmankatu 8 A
FIN-00290 Helsinki, Finland
Tel +358 (0)75 324 7016
Fax +358 (0)75 324 7099
anu.leinonen@licentia.fi
www.licentia.fi

May 8, 2006

Seppo Marttila
Maaniituntie 16
01900 Nurmijärvi

Hallo,

The patent process in regard to the APCI-purchase (Method and apparatus for mass spectrometric analysis of samples) to be commercialized in Licentia has entered the national stage. We have decided to apply for a patent at the European Patent Office, in Canada, in Japan as well as in the United States. For making the patent application pending we would need you to sign the enclosed authorization forms.

Could you, please, sign the documents and send them to me by May 22. Enclosed please find a return envelope.

If you have any questions regarding this matter, I will be happy to answer them.

Yours faithfully,

(Signature)

Anu Leinonen, Ph.D
Director, Life Sciences
Licentia Oy

LICENTIA

Licentia Ltd
Tukholmankatu 8 A
FIN-00290 Helsinki, Finland
Tel +358 (0)75 324 7016
Fax +358 (0)75 324 7099
anu.leinonen@licentia.fi
www.licentia.fi

8.5.2006

Seppo Marttila
Maaniituntie 16
01900 Nurmijärvi

Hei,

Licentiassa kaupallistettavana oleva APCI-hankkeen (Menetelmä ja laitteisto näytteiden tutkimiseksi massaspektrometrisesti) patentointiprosessi on edennyt kansalliseen vaiheeseen. Olemme päättäneet jatkaa patentointia Euroopan patenttivirastossa, Kanadassa, Japanissa ja Yhdysvalloissa. Patenttihakemusten vireille panemiseen liittyen, ohessa valtakirjoja, joihin tarvitsisimme allekirjoituksenne.

Voisitteko ystävällisesti allekirjoittaa dokumentit ja lähettää ne minulle takaisin 22.5. mennessä. Ohessa palautuskuori.

Vastaan mielelläni, jos teillä on asiasta kysyttävää.

Ystävällisin terveisin,

Anu Leinonen, Ph.D.
Director, Life Sciences
Licentia Oy

EXHIBIT C

Agreement on transfer of the immaterial rights in regard to the invention (draft)

I transfer without any financial compensation my part of the invention "miniaturized atmospheric chemical ionisation source" to Sami Franssila (University of Technology), Risto Kostiainen (University of Helsinki) and Tapio Kotiaho (University of Helsinki) such that each one of them gets one third (1/3) of my part (the part of Seppo Marttila 25%). However, Seppo Marttila is going to keep the copyright of the master's thesis regarding this subject.

The conditions for the realization of the transfer are:

1. The patent application has to be filed at the latest on November 14, 2003. Furthermore, the recipient of the transfer and the patent applicant have to accept the following issues regarding the carrying out in praxis and the publication of the master's thesis:
   - The professor supervising the master's thesis receives confidential information before the official release
   - The work is cased in by a commercial company prior to the official release
   - The receipt given by the National Board of Patents and Registration in regard to the filing of the patent application has to be delivered to Seppo Marttila at the latest on November 17, 2003. Hereafter a public presentation will take place and the maturity exam will be written.

2. The recipients of the transfer must see to that the transfer of the rights or the publication of the master's thesis does not infringe the rights of the sponsors of the project.

3. The recipients of the transfer are aware of the development stage of the invention prototype. Seppo Marttila does not commit himself on what in the invention is patentable.

For clarity reasons it has to be mentioned that if the patent application has not been filed by November 14, 2003, the invention part of Seppo Marttila will be returned to him. The master's thesis of Seppo Marttila will in any case be submitted for acceptance to the department council of the electrics department for the meeting on December 9, 2003.

Date: November 11, 2003 Place: Helsinki

Signature of the transferor

(Signature)

Seppo Marttila

Signatures of the recipients of the transfer

(Signature) Sami Franssila	(Signature) Risto Kostiainen	(Signature) Tapio Kotiaho

Enclosures: Employment invention declaration including enclosures and the statement of the University of Technology

Sopimus keksintöön liittyvien immateriaalioikeuksien luovuttamisesta (luonnos)

Siirrän ilman rahallista vastiketta osuuteni miniatyrisoitu ilmanpainekemiallinenionisaatiolähde"-keksinnöstä Sami Franssilalle (TKK), Risto Kostiaiselle (HY) ja Tapio Kotiaholle (HY) siten, että kukin heistä saa yksi kolmasosaa (1/3) osuudestani (Seppo Marttilan osuus 25%). Seppo Marttilalla säilyy kuitenkin tekijänoikeus aiheeseen liittyvään diplomityöhön.

Siirron toteutumisen ehtoina on:

1. Patenttihakemus on jätettävä viimeistään 14.11.2003. Luovutuksen saajan ja patenttia hakevan tahon on lisäksi hyväksyttävä seuraavat diplomityön käytännön suorittamiseen ja julkistamiseen liittyvät seikat:
   - Diplomityötä valvova professori saa luottamuksellista tietoa haltuunsa ennen virallista julkistusta
   - Työ kansitetaan kaupallisessa firmassa ennen virallista julkistusta
   - Patenttihakemuksen jättämisestä on toimitettava PRH:n antama kuitti Seppo Marttilalle viimeistään 17.11.2003. Tämän jälkeen aiheesta pidetään julkinen esitelmä ja kirjoitetaan kypsyysnäyte.

2. Luovutuksen saajien on huolehdittava siitä, että oikeuksien siirto tai diplomityön julkaiseminen eivät loukkaa projektin rahoittajien oikeuksia.

3. Luovutuksen saajat ovat tietoisia keksintöprototyypin kehitysasteesta. Siihen, mikä keksinnössä on patentoitavissa, Seppo Marttila ei ota kantaa.

Selvyyden vuoksi todetaan, että mikäli patenttihakemusta ei ole jätetty 14.11.2003 mennessä, Seppo Marttilan osuus keksinnöstä palautuu hänelle. Seppo Marttilan diplomityö jätetään kaikissa tapauksissa hyväksyttäväksi sähköosaston osastoneuvoston 9.12.2003 pidettävään kokoukseen.

Aika 11.11.03 Paikka Helsinki

Siirtäjän allekirjoitus

Seppo Marttila

Luovutuksen saajien allekirjoitukset

Sami Franssila Risto Kostiainen Tapio Kotiaho

Liitteet: Työsuhdekeksintöilmoitus liitteineen ja TKK:n lausunto

Translation from Finnish

CONTRACT OF SALE

1. SELLER

Risto Kostiainen (date of birth 7.4.1955)
Väinö Auerinkatu 7 F 72
00560 Helsinki

Tapio Kotiaho (date of birth 14.10.1958)
Otsonkallio 3 S 139
02110 Espoo

Samuli Franssila (date of birth 8.7.1959)
Tukholmankatu 7 C 19
00270 Helsinki

2. BUYER

Licentia Oy (Business Identity Code 1639532-6)
Erottajankatu 19 B 5
00130 Helsinki
Tel. (09) 6814 9570
fax (09) 6814 9599

Henceforth the Seller and the Buyer are together referred to as the "Parties"

3. UNIVERSITIES AND LABORATORIES ENTITLED TO THE PURCHASE PRICE SHARE

University of Helsinki (Helsingin yliopisto)
Institute of Pharmacy/DDTC
00014 Helsingin yliopisto

University of Technology (Teknillinen korkeakoulu)
Microelectronics Center (Mikroelektroniikka keskus)
PL 1000
02015 TKK

4. DEFINITIONS

In this contract of sale including its enclosures the following terms are consistently used in the following way:

By "research results" is meant the material, data, know-how, innovations as well as the immaterial rights associated herewith created during the Seller's research.

---

5. OBJECT OF PURCHASE

The object of purchase is the research results named "**APCI –chip**" owned by the Seller Risto Kostiainen, Tapio Kotiaho and Sami Franssila as well as the immaterial rights associated therewith (henceforth "Technology" ("Teknologia")). Technology is more precisely defined in enclosure 1. The total transfer of the copyrights associated with the Technology also includes amending and forwarding rights.

---

8. TRANSFER OF OWNERSHIP

The right of ownership of the object of purchase is transferred when both the Seller and the Buyer have signed this contract of sale.

SIGNATURES

This contract of sale has been prepared in four (4) identical originals, one for each Seller and one for Licentia.

Helsinki October 29, 2003	Helsinki November 11, 2003
LICENTIA OY	
(Signature)	(Signature)
Timo Törmälä Managing Director	Risto Kostiainen
Helsinki November 11, 2003	Helsinki November 11, 2003
(Signature)	(Signature)
Tapio Kotiaho	Sami Franssila

ENCLOSURES
1. A more precise definition of the Technology and the immaterial rights associated herewith
2. Collaboration contract related to the purchase between the Seller and the Buyer
3. Distribution of the right of ownership and of the beneficiary income as to the Seller and the Inventors
4. A list of the Inventor's publications, releases and performances in regard to the Technology
5. Extract from the trade register of the Buyer

ENCLOSURE 1

The Technology comprises a miniaturized APCI (atmospheric pressure chemical ionisation)- ion source enabling the analysis of samples of small amounts, for example, in mass spectrometric implementations.
A more precise description of the Technology is to be found in the FI/US patent application filed in November 2003.

KAUPPAKIRJA

1. MYYJÄ

Risto Kostiainen (synt.aika 7.4.1955)
Väinö Auerinkatu 7 F 72
00560 Helsinki

Tapio Kotiaho (synt.aika 14.10.1958)
Otsonkallio 3 S 139
02110 Espoo

Samuli Franssila (synt.aika 8.7.1959)
Tukholmankatu 7 C 19
00270 Helsinki

2. OSTAJA

Licentia Oy (Y-tunnus 1639532-6)
Erottajankatu 19 B 5
00130 Helsinki
puh. (09) 6814 9570
faksi (09) 6814 9599

Myyjästä ja Ostajasta käytetään jäljempänä yhteisnimitystä "Osapuolet"

3. KAUPPAHINTAOSUUTEEN OIKEUTETUT YLIOPISTOT JA LABORATORIOT

Helsingin yliopisto
Farmasian laitos/DDTC
00014 Helsingin yliopisto

Teknillinen korkeakoulu
Mikroelektroniikka keskus
PL 1000
02015 TKK

4. MÄÄRITELMÄT

Tässä kauppakirjassa ja sen liitteissä käytetään johdonmukaisesti seuraavia termejä tarkoittamaan seuraavanlaisia asioita:

"Tutkimustulokset" tarkoittavat Myyjän tutkimuksen aikana ja tuloksena syntynyttä materiaalia, tietoa, tietotaitoa, keksintöjä ja niihin liittyviä immateriaalioikeuksia.

"Asiakas" tarkoittaa kolmatta ulkopuolista osapuolta, joka hyödyntää jollain tavalla tutkimustuloksia myönnetyn vastikkeellisen käyttöoikeuden nojalla tai joka ostaa kaikki oikeudet tutkimustuloksiin.

"Hyödyntämistulo" tarkoittaa kaikenlaisia rahasuorituksia (muun muassa alkumaksut, rojaltit, vähimmäisrojaltit, osakkeista saatavat osingot, osakkeiden myynnistä saatavat myyntitulot), joita asiakas suorittaa vastikkeena saamastaan käyttö- tai omistusoikeudesta tutkimustuloksiin.

"Ulkoiset kustannukset" tarkoittavat kustannuksia, jotka Licentia maksaa Myyjälle tai ulkopuoliselle taholle niiden tutkimustuloksiin liittyvien tehtävien suorittamisesta. Ulkoiset kustannukset on määritelty tämän sopimuksen kohdassa 6.

"Sisäiset kustannukset" tarkoittavat Licentian palveluksessa olevan henkilöstön palkka- ja sosiaalikustannuksia sekä Licentian toimintaan liittyviä yleiskustannuksia.

"Teknologiansiirtosopimus" tarkoittaa asiakkaan ja Licentian solmimaa tutkimustulosten hyödyntämiseen perustuvaa sopimusta, jossa Licentia myöntää asiakkaalle käyttöoikeuden tutkimustuloksiin tietyillä ehdoilla tai kaikki oikeudet tutkimustuloksiin.

"Tutkimussopimus" tarkoittaa jatkotutkimukseen liittyvää sopimusta, jossa Licentia, Myyjä/Myyjän yliopisto ja kolmas osapuoli sopivat Myyjän suorittamasta jatkotutkimuksesta.

"Immateriaalioikeudet" tarkoittavat yksinoikeuksia, jotka antavat haltijalleen tiettynä määräaikana mahdollisuuden kieltää muita käyttämästä tai hyödyntämästä hyväksee ammattimaisesti suojan kohdetta. Immateriaalioikeuksiin kuuluvat sekä teollisoikeudet että tekijänoikeudet.

"Teollisoikeudellinen suojaus" tarkoittaa tutkimustulosten oikeuksien haltijan hakemuksesta hänelle valtiovallan myöntämää teollisoikeussuojaa tutkimustuloksilleen kuten muun muassa patenttia, hyödyllisyysmallia, mallia ja/tai tavaramerkkiä.

"Välitön vahinko" tarkoittaa vahingosta aiheutuneita toteennäytettyjä suoria kuluja ja kustannuksia, jotka ovat syntyneet Osapuolen olennaisen sopimusrikkomuksen seurauksena toiselle Osapuolelle.

"Välillinen vahinko" tarkoittaa vaikeasti ennalta arvattavissa olevaa vahinkoa, muun muassa liikevaihdon vähentymisestä tai keskeytymisestä aiheutuvaa vahinkoa tai saamatta jäänyttä voittoa.

5. KAUPAN KOHDE

Kaupan kohteena on Myyjän Risto Kostiaisen, Tapio Kotiahon ja Sami Franssilan omistamat tutkimustulokset nimeltään **"APCI –chip"** ja niihin liittyvät immateriaalioikeudet (jäljempänä "Teknologia"). Teknologia on tarkemmin määritelty liitteessä 1. Teknologiaan liittyvien tekijänoikeuksien kokonaisluovutukseen sisältyy myös muuttamis- ja edelleenluovutusoikeudet.

6. KAUPPAHINTA

Kauppahintana Ostaja suorittaa Teknologian hyödyntämisestä saamistaan nettohyödyntämistuloista

1) Myyjälle 1/3 ja
2) Myyjän yliopistoille/laboratorioille yhteensä 1/3 siten, että Helsingin yliopiston ja Teknillisen korkeakoulun osuudet jakautuvat keskenään HY 50% ja TKK 50%

niin kauan kuin Teknologia tuottaa hyödyntämistuloa.

Koska omistusoikeus jakautuu Myyjän puolella useammalle henkilölle, Myyjän nettohyödyntämistulo-osuudet jaetaan tasan heidän kesken heidän solmimansa tulonjakosopimuksen perusteella, joka on tämän kauppakirjan liitteenä 3.

Teknologian nettohyödyntämistulot määritellään siten, että asiakkaan maksamasta hyödyntämistulosta vähennetään arvonlisävero ja muut mahdollisesti hyödyntämistuloihin liittyvät verot ja Ostajan todennettavissa olevat Teknologiaan liittyvät ulkopuoliset kustannukset, jotka ovat jo syntyneet sekä jotka syntyvät yhden vuoden sisällä suoritusajankohdasta lukien. Vähennyskelpoisia ovat Ostajan ulkoiset kustannukset, jotka ovat aiheutuneet:

- Teknologian arvioinnin aikana,
- Teknologian patentoinnista ja muusta teollisoikeudellisesta suojaamisesta sekä niihin liittyvistä prosesseista,
- Teknologian kaupallistamisesta, teknologiansiirtosopimusneuvotteluista ja -laadinnasta,
- Licentian käyttämistä ulkopuolisten asiantuntijoiden ja agenttien palveluista,
- Teknologiansiirtosopimuksista tai niiden tulkinnasta syntyneistä riitaisuuksista, sopimusehtojen noudattamisesta tai valvomisesta ja näihin liittyvistä neuvotteluista, oikeudenkäynneistä, välimiesoikeusmenettelystä ja saatavien perinnästä sekä kaikkiin näihin käytetyistä lakiasiantuntijoiden ja asianajajien palveluista,
- Teknologiaan liittyvien teollisoikeuksien puolustamisesta ja kolmannen osapuolen väitteisiin vastaamisesta, niihin liittyvistä neuvotteluista, oikeudenkäynneistä ja välimiesmenettelystä ja niissä käytettävien patenttiasiamiesten ja lakiasiantuntijoiden palveluista, täytäntöönpanokelpoisten tuomioiden ja päätösten mukaisten vahingonkorvausten suorittamisesta teknologiansiirtosopimusosapuolelle tai kolmannelle osapuolelle sekä
- muita mahdollisia Osapuolten myöhemmin erikseen kirjallisesti ennalta sovittuja kustannuksia, joista tehdään erilliset selvitykset tämän kauppakirjan liitteiksi.

7. KAUPPAHINNAN SUORITUS JA MYYJÄN OIKEUS TARKASTAA KAUPPAHINTASUORITUSTEN OIKEELLISUUS

Ostaja on velvollinen toimittamaan Myyjälle sekä Helsingin yliopistolle ja Teknilliselle korkeakoululle samanlaiset ilmoitukset kertyneistä brutto- ja nettohyödyntämistuloista vähennettävine kustannuserittelyineen vuosittain seuraavan vuoden 7.1. mennessä ajanjaksolta 1.1. – 31.12. Mikäli kertyneet bruttohyödyntämistulot kattavat Ostajan edellä kohdassa 6 mainitut kustannukset, Ostaja on velvollinen tilittämään Myyjälle tämän nettohyödyntämistulo-osuuden vähennettynä kulloinkin voimassaolevan verolainsäädännön edellyttämillä vähennyksillä Myyjän ilmoittamalle tilille 21.1 mennessä sekä velvollinen lähettämäänsä ilmoitukseen perustuen maksamaan Helsingin yliopiston ja Teknillisen korkeakoulun nettohyödyntämistulo-osuuden niiden lähettämien erillisten laskujen mukaisesti.

Myyjällä tai hänen määräämällä tilintarkastajalla on oikeus Myyjän kustannuksella tarkastaa Ostajan kirjanpitoon ja tilityksiin siltä osin kuin kauppahinnan suorittamisen valvomisen kannalta on tarpeellista. Tarkistamispyyntö on lähettävä kirjallisesti Ostajalle viimeistään seitsemän (7) päivää ennen tarkistusajankohtaa, ja tarkistamisen on tapahduttava virallisena työaikana. Myyjä vastaa Ostajalle tarkastamisesta aiheutuneista Ostajan sisäisistä kustannuksista, mikäli tilityksistä ei löydy olennaisia virheellisyyksiä. Ostaja on velvollinen suorittamaan kaikki tarkastuksen aiheuttamat kustannukset siinä tapauksessa, että kirjanpidossa tai tilitetyissä nettohyödyntämistuloissa havaitaan laiminlyöntejä tai puutteellisuuksia, jotka aiheuttavat vähintään viiden (5) prosentin poikkeaman oikeasta suorituksesta.

8. OMISTUSOIKEUDEN SIIRTYMINEN

Omistusoikeus kaupan kohteeseen siirtyy samalla, kun sekä Myyjä että Ostaja ovat allekirjoittaneet tämän kauppakirjan.

9. MYYJÄN VAKUUTUS JA VELVOLLISUUS LUOVUTTAA KAUPAN KOHDETTA KOSKEVA MATERIAALI

Myyjä vakuuttaa, että hänellä on parhaan tietämyksensä mukaan kaikki oikeudet Teknologiaan ja että hän on oikeutettu yksin määräämään niistä. Myyjä vakuuttaa, että kukaan kolmas osapuoli ei ole esittänyt vaatelta tai väitteitä paremmasta oikeudesta Teknologiaan ja että Teknologiaa ei ole saatettu julkisuuteen, mikäli kaupan kohteelle ei ole vielä haettu patenttisuojaa. Teknologiaa kehittämässä ollut yksi keksijä Seppo Marttila on luovuttanut omistusoikeusosuutensa Myyjälle liitteenä 3 mukaisella asiakirjalla eikä hänellä ole vaatimuksia Teknologiaan.

Myyjä vakuuttaa, ettei hän ole saattanut tai saata kolmansien osapuolten tietoon millään tavalla Teknologiaan liittyviä tietoja, jotka voivat estää Teknologiaan liittyvien patenttien myöntämisen jossain maassa. Myyjän on annettava Ostajalle tiedoksi ennen kaupantekohetkeä kaikki mahdolliset julkaisut, julkistamiset ja Myyjän pitämät suulliset esitykset, jotka liittyvät Teknologiaan (luettelo liitteenä 4).

Myyjä on velvollinen kaupantekohetkellä luovuttamaan Ostajalle kaikki kaupan kohteeseen liittyvät ja sen teollisoikeudelliseen suojaamiseen vaadittavat asiakirjat, piirustukset, suunnitelmat, muun materiaalin ja kaiken tiedon, jolla saattaa olla merkitystä patenttihakemuksen hyväksymisen, markkinoimisen tai kaupallistamisen kannalta. Myyjä on velvollinen allekirjoittamaan kaikki sopimuksen kohteeseen liittyvät teollisoikeudellisen suojan saamiseksi vaaditut siirtokirjat.

Mikäli Ostaja myöhemmin toteaa, että Myyjä on vastoin tässä kohdassa mainittua vakuutustaan salannut Ostajalta edellä mainittuja tietoja eikä siitä syystä kykene saamaan Teknologialle teollisoikeussuojaa, kaupallistamaan Teknologiaa tai Ostaja joutuu tästä syystä maksamaan kolmansille osapuolille vahingonkorvauksia, Myyjä on velvollinen korvaamaan Ostajalle kohdassa 11 mainitut Ostajalle aiheutuneet välittömät vahingot.

10. MYYJÄN OIKEUDET TIETEELLISEEN TUTKIMUS- JA JULKAISUTOIMINTAAN JA SALASSAPITOVELVOLLISUUS

Myyjällä on oikeus tehdä Teknologiaan liittyvää tieteellisistä tutkimusta ja julkaista tutkimustuloksia, mikäli julkaiseminen/julkistaminen ei vaaranna mahdollisuutta saada Teknologialle teollisoikeussuojaa. Myyjä on kuitenkin velvollinen kirjallisesti informoimaan Ostajaa kaupan kohteeseen liittyvien tulevien julkaisujen/julkistamisien sisällöstä viimeistään yhtä (1) kuukautta ennen suunniteltua julkaisuajankohtaa/julkistamista.

Mikäli julkaisumateriaalissa on tietoa, jonka julkaiseminen vaarantaa Teknologiaan kohdistuvan patenttisuojan saamisen, Myyjä on velvollinen Ostajan pyynnöstä lykkäämään julkaisuajankohtaa siksi ajaksi, että teollisoikeushakemus saadaan vireille, kuitenkin enintään kolme (3) kuukautta. Edellä

mainitusta huolimatta Teknologian keksijänä oleva Seppo Mantila saa julkistaa Teknologiaan liittyvän diplomityönsä 14. marraskuuta 2003 jälkeen.

Myyjä on velvollinen olemaan paljastamatta kolmansille osapuolille Teknologian patentointiin liittyviä tietoja ja kaupallistamiseen liittyviä liikesalaisuuksiksi katsottavia tietoja, jotka voivat vaarantaa Ostajan oikeuksia tai Teknologian kaupallistamista. Mikäli Myyjä haluaa luovuttaa kolmansille osapuolille tällaista luottamuksellista tietoa, on Myyjä velvollinen etukäteen neuvottelemaan luovutuksesta Ostajan kanssa. Mikäli Ostaja antaa suostumuksensa Myyjälle luottamuksellisen tiedon luovuttamiseen, Ostaja laatii salassapitosopimuksen, jonka kolmas osapuoli on velvollinen allekirjoittamaan ennen luottamuksellisen tiedon luovutusta. Myyjä on velvollinen pitämään salassa Licentian liike- ja yrityssalaisuudet sekä Licentian Myyjälle esittämät teknologiansiirtosopimusehdotus -ehdotukset ja solmitut teknologiansiirtosopimukset kaikkine ehtoineen.

11. VASTUUNRAJOITUKSET

Ostaja ei vastaa siitä, jos se ei onnistu kaupallistamaan Teknologiaa eikä siitä millä ehdoilla Teknologia kaupallistetaan. Mikäli Ostaja on kuitenkin olennaisesti rikkonut tämän kauppakirjan ja yhteistyösopimuksen mukaisia ehtoja, Ostaja vastaa tahallaan tai tuottamuksellaan Myyjälle aiheuttamistaan välittömistä vahingoista. Ostaja ei vastaa välillisistä vahingoista. Ostajan tämän kauppakirjan ja yhteistyösopimuksen mukainen vastuu rajoittuu kuitenkin kaikissa tapauksissa enintään sihen rahamäärään, jonka Ostaja on saanut Teknologian nettohyödyntämistuloista osuutenaan.

Mikäli Myyjä on olennaisesti rikkonut tämän sopimuksen mukaisia ehtoja, Myyjä vastaa tahallaan tai tuottamuksellaan aiheuttamistaan välittömistä vahingoista Ostajalle. Välittöminä vahinkoina pidetään Ostajalle aiheutuneita kohdan 6 mukaisia ulkoisia ja Ostajan sisäisiä palkkakustannuksista, jotka ovat aiheutuneet tämän sopimuksen mukaisten velvollisuuksien hoitamisesta, sekä sitä Ostajan saamatta jäänyttä nettohyödyntämistulo-osuutta ja palkkiota, johon Ostajalla on oikeus tämän sopimuksen perusteella. Myyjä ei vastaa välillisestä vahingoista.

12. MYYJÄN OIKEUS OSTAA KAUPAN KOHDE TAKAISIN

Mikäli Ostaja ei ole saanut kaupallistettua kaupan kohdetta ja mikäli Ostaja päättää luopua kaupan kohteeseen liittyvistä immateriaalioikeuksista, Ostaja on velvollinen ilmoittamaan kirjallisesti Myyjälle kolmea (3) kuukautta ennen kuin Ostaja lopettaa kaupan kohteen patentoimisprosessin ja siihen liittyvän kustannusvastuunsa. Myyjällä on tänä kolmen kuukauden aikana oikeus ostaa kaupan kohde kaikkine oikeuksineen ja velvollisuuksineen takaisin Osapuolten sopimilla ehdoilla kohtuullisesta korvausta vastaan. Mikäli Myyjä ei ole ostanut kaupan kohdetta ja maksanut siitä sovittua korvausta Ostajalle kolmen kuukauden kuluessa siitä hetkestä lukien kun Ostaja on lähettänyt Myyjälle kirjallisen ilmoituksen päätöksestään lopettaa kaupan kohteen patentoimisprosessin jatkamisen, Ostaja on oikeutettu lopettamaan kaupan kohteeseen liittyvien patenttihakemusten ja patenttien ylläpitämisen.

Myyjällä on etu-oikeus ostaa kaupan kohde, mikäli Ostaja asetetaan konkurssiin tai lopettaa toimintansa.

13. MYYJÄN JA OSTAJAN VÄLINEN YHTEISTYÖ

Myyjä ja Ostaja sopivat Teknologiaan liittyvästä yhteistyöstä tämän kauppakirjan liitteenä olevan Yhteistyösopimuksen ehtojen mukaisesti (liite 2). Yhteistyösopimus tulee voimaan Osapuolia sitovana tämän kauppakirjan allekirjoittamisella.

14. FORCE MAJEURE

Osapuoli ei voi vaatia toiselta Osapuolelta tämän kauppakirjan ja sen liitteenä olevan yhteistyösopimuksen täyttämistä eikä niiden täyttämättä jäämisestä aiheutuneesta vahingosta vahingonkorvausta, mikäli niiden täyttämisen estää tai tekee kohtuuttoman vaikeaksi ylivoimainen este eli sellainen ennalta arvaamaton tapahtuma, joka sattuu sopimuksen voimaantulon jälkeen, ja johon osapuolet eivät voi itse mitenkään vaikuttaa. Esteen syntymisestä ja sen lakkaamisesta on Osapuolten ilmoitettava välittömästi kirjallisesti toisilleen. Osapuoli, joka on vedonnut ylivoimaiseen esteeseen, on velvollinen näyttämään toteen sen vaikutus sopimuksen täyttämiseen.

15. ERIMIELISYYKSIEN RATKAISEMINEN

Tästä kauppakirjasta ja sen liitteenä olevasta yhteistyösopimuksesta osapuolten tulkinnasta aiheutuneet erimielisyydet tai riitaisuudet pyritään ratkaisemaan ensisijaisesti osapuolten välisillä neuvotteluilla ja sen jälkeen Suomen Asianajoliiton sovintomenettelyssä. Mikäli sovintoon ei kuitenkaan päästä, erimielisyydet ratkaistaan lopullisesti yhden välimiehen välimiesmenettelyssä Keskuskauppakamarin välityslautakunnan sääntöjen mukaisesti salassapitovelvollisuutta noudattaen. Jos kuitenkin erimielisyys koskee ainoastaan saatavaa, riita ratkaistaan ensi asteessa Helsingin käräjäoikeudessa.

16. OSTAJAN TIEDONANNOT

Ostaja antaa tiedoksi tämän kauppakirjan pääsisällön Helsingin yliopistolle ja Teknilliselle korkeakoululle.

ALLEKIRJOITUKSET

Tätä kauppakirjaa on laadittu neljä (4) samasanaista kappaletta, yksi kullekin Myyjälle ja yksi Licentialle.

Helsingissä 29 lokakuuta 2003

LICENTIA OY

Timo Törmälä
Toimitusjohtaja

Helsingissä 11 marras lokakuuta 2003

Risto Kostiainen

Helsingissä 11 marras lokakuuta 2003

Tapio Kotiaho

Helsingissä 11 marras lokakuuta 2003

Sami Franssila

LIITTEET:

1. Teknologian tarkempi määrittely ja siihen liittyvät immateriaalioikeudet
2. Kauppaan liittyvä Myyjän ja Ostajan välinen yhteistyösopimus
3. Omistusoikeuden ja hyödyntämistulon jakautuminen Myyjän ja keksijöiden osalta
4. Luettelo Teknologiaan liittyvistä Tutkijan julkaisuista, julkistamisista ja esityksistä
5. Ostajan kaupparekisteriote

LIITE 2

MYYJÄN JA OSTAJAN VÄLINEN YHTEISTYÖSOPIMUS

1. SOPIMUKSEN KOHDE JA TARKOITUS

Tämän sopimuksen kohteena on kauppakirjassa mainittu kaupan kohde.

Tämän yhteistyösopimuksen tarkoituksena on Myyjän ja Ostajan välinen yhteistyö jäljempänä mainituin ehdoin, jotta Teknologialle onnistutaan saamaan Ostajan määrittelemä teollisoikeussuoja, jotta Teknologia saadaan kaupallistettua ja jotta Teknologiaan liittyviä teollisoikeuksia voidaan puolustaa.

2. MYYJÄN VELVOLLISUUDET

Myyjä sitoutuu kohtuullisessa määrin yhteistyöhön Ostajan kanssa turvatakseen ja suojatakseen tämän yhteistyösopimuksen mukaisen tarkoituksen ja Ostajan oikeudet. Myyjä sitoutuu Ostajan erityisestä pyynnöstä osallistumaan teknologiansiirtosopimusneuvotteluihin Teknologian asiantuntijana, antamaan apuaan patenttihakemuksien laatimisessa ja välipäätöksiin vastaamisessa, jotta patentit tullaan myöntämään, sekä patenttien puolustamisessa. Mikäli Myyjälle aiheutuu merkittäviä kustannuksia antamastaan teknisestä avusta, Myyjä on oikeutettu saamaan Osapuolten erikseen sopiessa kohtuullisen korvauksen antamastaan työpanoksestaan Teknologian asiantuntijana tai avustajana, jota Ostaja on pyytänyt. Kyseiset kustannukset ovat vähennettävissä olevia kustannuksia kauppakirjan mukaisesti.

Myyjä on velvollinen ilmoittamaan viivytyksettä Ostajalle kaikki tietoonsa tulleet toimet, jotka mahdollisesti loukkaavat Teknologiaan liittyviä patenttihakemuksia tai patentteja.

Mikäli kolmas osapuoli väittää Teknologiaan liittyvän patenttihakemuksen tai patentin loukkaavan hänen oikeuttaan, Ostaja päättää neuvoteltuaan ensin Myyjän kanssa, miten se suhtautuu esitettyihin vaatimuksiin ja miten mahdollisia oikeudenkäyntejä hoidetaan. Mikäli kolmas taho loukkaa Teknologiaan liittyvää patenttihakemusta tai patenttia, Ostaja päättää neuvoteltuaan ensin Myyjän kanssa suhtautumisestaan loukkaukseen ja mahdollisesta loukkauskanteen vireille saattamisesta tuomioistuimeen. Mikäli Ostaja päättää aloittaa edellä mainittuihin asioihin liittyvät neuvottelut kolmannen osapuolen kanssa tai päättää aloittaa oikeudenkäyntiprosessit, Myyjä on velvollinen avustamaan työpanoksellaan Ostajaa Teknologiaan liittyvien patenttien ja patenttihakemusten puolustamisessa ja kolmansien osapuolten esittämien vaatimusten torjumisessa ja niihin liittyvissä oikeudenkäynneissä. Mikäli kyseinen avustaminen vaatii Myyjältä merkittävää työpanostusta, Myyjä on oikeutettu saamaan Osapuolten erikseen sopiman kohtuullisen korvauksen tekemästään työstä. Edellä mainittu korvaus on vähennettävissä kauppakirjan mukaisesti hyödyntämistuloista.

Myyjä on velvollinen säilyttämään Teknologiaan liittyvät asiakirjat todistusaineistona niin kauan kuin Teknologiaan liittyvät teollisoikeudet ovat voimassa.

Myyjällä on velvollisuus jatkaa Teknologian jatkotutkimusta Ostajan toimeksiannosta, mikäli Osapuolet sopivat siitä erikseen kirjallisesti.

Mikäli Ostajan solmimien teknologiansiirtosopimusten osana asiakas haluaa Teknologiaan liittyvää Myyjän tietotaitoa ja edellyttää Myyjältä jatkotutkimuksen suorittamista, Myyjä on velvollinen suorittamaan asiakkaan kanssa sovittavaa jatkotutkimustyötä Myyjän ja Ostajan yhdessä neuvotteleman ja allekirjoitettavan tutkimussopimuksen mukaisesti.

Sillä henkilöllä myyjistä, joka muuttaa Suomen ulkopuolelle tai ulkomailla, on velvollisuus ilmoittaa Ostajalle osoitteenmuutoksestaan.

3. OSTAJAN VELVOLLISUUDET

Ostaja vastaa Teknologian teollisoikeudellisesta suojaamisesta ja sitoutuu hakemaan patentteja, jatkamaan vireillä olevia patenttihakemuksia ja ylläpitämään myönnettyjä patentteja niissä maissa, joissa Ostaja katsoo sen olevan tarkoituksenmukaista Teknologian kaupallistamiseksi. Ostaja on oikeutettu päättämään teollisoikeudellisen suojan laajuudesta.

Ostaja sitoutuu parhaan kykynsä mukaan kaupallistamaan Teknologian. Ostaja vastaa harkitsemallaan tavalla Teknologian kaupallistamisesta.

Ostaja on velvollinen informoimaan Myyjää Teknologian teollisoikeudellisesta suojaamisesta, solmituista teknologiansiirtosopimuksista ja toimittamaan allekirjoitetuista sopimuksista kopiot Myyjälle Myyjän sitä erikseen pyytäessä. Mikäli Ostaja on velvollinen suorittamaan kauppahintaa myös Myyjän yliopistolle/laboratoriolle, Ostajalla on velvollisuus ilmoittaa myös näille tahoille solmitut teknologiansiirtosopimukset.

Mikäli Ostaja on järjestänyt Myyjälle/Myyjän yliopistolle tutkimustoimeksiannon Teknologian jatkotutkimukseen tai mikäli asiakkaan ja Ostajan väliseen teknologiansiirtosopimukseen liittyy olennaisena osana jatkotutkimussopimus kyseisen asiakkaan kanssa, Licentia on oikeutettu saamaan edellä mainittujen tutkimussopimusten mukaisesta tutkimusrahasta palkkion, joka on viisitoista (15) prosenttia kokonaistutkimusrahoituksesta. Licentian palkkio tulee sisällyttää maksettavaan tutkimusrahoitukseen erillisenä liitynnäisenä kustannuseränä. Myyjä on velvollinen huolehtimaan siitä, että Myyjän yliopisto maksaa välittömästi Licentialle edellä mainitun palkkion asiakkaan maksettua kyseisen tutkimusrahan Myyjän yliopistolle.

4. MYYJÄN OIKEUS ESITTÄÄ NÄKÖKANTANSA TEKNOLOGIANSIIRTOSOPIMUSLUONNOKSIIN

Myyjällä on oikeus esittää mielipiteensä Ostajan esittämistä teknologiansiirtosopimusluonnoksista. Mikäli Myyjällä on painavia perusteluita miksi Ostajan tulisi pidättäytyä solmimasta kyseistä sopimusta, Ostaja pyrkii ottamaan huomioon Myyjän esittämät perustelut arvioidessaan solmiiko se kyseisen teknologiansiirtosopimuksen.

5. SALASSAPITOVELVOLLISUUS

Luottamuksellista tietoa on kaikki se missä muodossa tahansa ilmaistu tieto, jonka kumpi tahansa Osapuoli on merkinnyt luottamukselliseksi tiedoksi ja ilmoittanut kirjallisesti siitä toiselle osapuolelle. Jos luottamuksellinen tieto on annettu suullisesti, Osapuolen on välittömästi kirjattava luottamuksellinen tieto kirjalliseen muotoon ja lähetettävä se tiedoksi toiselle Osapuolelle. Luottamuksellisen tiedon vastaanottaja on velvollinen pitämään luottamuksellisen tiedon salassa viisi (5) vuotta sen vastaanottohetkestä lukien, ellei luovutettu luottamuksellinen tieto ole tullut sitä ennen julkiseksi ilman luottamuksellisen tiedon vastaanottajan tämän kohdan vastaista toimintaa. Edellä mainitusta huolimatta Licentia on kuitenkin oikeutettu luovuttamaan salassapitosopimusta vastaan luottamuksellista tietoa potentiaalisille asiakkaille Teknologian kaupallistamistarkoituksessa.

Myyjä sitoutuu olemaan paljastamatta Ostajan liike- ja yrityssalaisuuksia. Myyjä on velvollinen pitämään salassa Ostajan hänelle esittämät teknologiansiirtosopimusehdot, teknologiansiirtosopimusehdotukset ja solmitut teknologiansiirtosopimukset kaikkine ehtoineen.

6. OLENNAINEN SOPIMUSRIKKOMUS

Mikäli Ostaja on olennaisesti rikkonut tämän yhteistyösopimuksen mukaisia ehtoja, Ostaja vastaa tahallaan tai tuottamuksellaan Myyjälle aiheuttamistaan välittömistä vahingoista. Ostaja ei vastaa välillisistä vahingoista. Ostajan tämän yhteistyösopimuksen mukainen vastuu rajoittuu kuitenkin kaikissa tapauksissa enintään siihen rahamäärään, jonka Ostaja on saanut Teknologian nettohyödyntämistuloista osuutenaan.

Mikäli Myyjä on olennaisesti rikkonut tämän yhteistyösopimuksen mukaisia ehtoja, Myyjä vastaa tahallaan tai tuottamuksellaan aiheuttamistaan välittömistä vahingoista Ostajalle. Välittöminä vahinkoina pidetään Ostajalle aiheutuneita kauppakirjan kohdan 6 mukaisia ulkoisia ja Ostajan sisäisiä palkkakustannuksista, jotka ovat aiheutuneet kauppakirjan ja tämän sopimuksen mukaisten velvollisuuksien hoitamisesta, sekä siitä Ostajan saamatta jäänyttä nettohyödyntämistulo-osuutta ja palkkiota, johon Ostajalla on oikeus kauppakirjan ja tämän sopimuksen perusteella. Myyjä ei vastaa välillisestä vahingoista.

7. SOPIMUKSEN SIIRTÄMINEN

Myyjällä ei ole oikeutta siirtää tätä sopimusta eikä sen osaa kolmannelle ilman Ostajan erillistä etukäteistä kirjallista hyväksyntää.

8. SOPIMUKSEEN TEHTÄVÄT MUUTOKSET

Sopimukseen tehtävät muutokset on tehtävä kirjallisesti ja muutokset on Osapuolten allekirjoituksilla vahvistettava sekä otettava tämän sopimuksen liitteeksi. Muutoksissa yhteydessä on mainittava selkeästi, että muutoksilla on tarkoitus muuttaa tätä sopimusta.

9. SOPIMUKSEN VOIMASSAOLO

Tämä sopimus on voimassa niin kauan kuin Ostajalla on omistusoikeudet Teknologiaan. Tämän sopimuksen voimassaoloaikana tehdyt teknologiansiirtosopimukset ja tutkimussopimukset jäävät voimaan sellaisenaan myös tämän sopimuksen päättymisen jälkeenkin.

LIITE 1

Teknologia käsittää miniatyrisoidun APCI (atmospheric pressure chemical ionisation)-ionilähteen, joka mahdollistaa pienten näytemäärien analysoinnin mm. massaspektrometrisiin sovelluksiin. Teknologian tarkempi kuvaus löytyy marraskuussa 2003 jätettävästä FI/US-patenttihakemuksesta.